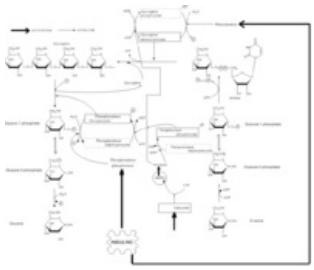
Starvation and disorders of ketone body production

High levels of insulin and glucose in the blood inhibit lipolysis after eating. During the transition from a saturated state to starvation (lowering blood glucose levels), the liver glycogen begins to burn. The level of insulin decreases (stops blocking lipolysis) and the level of glucagon in the blood rises. Fat is mobilized in the form of free fatty acids and glycerol released into the plasma. Free fatty acids taken up by tissues are processed by β-oxidation or esterification. Glycerol is involved in gluconeogenesis. When the mentioned energy sources are not enough to keep up with energy consumption, there is an increased formation of ketone bodies, which are **easier to oxidize** than free fatty acids. Ketogenesis takes place in the **[mitochondria | mitochondria]] of the liver** and the ketone bodies are consumed in the mitochondria of extrahepatic tissues. Ketone bodies are *acetoacetate*, *3-hydroxybutyrate* and *acetone* which are soon exhaled.

- In the case of *fatty acid metabolism* and *ketone synthesis*, which are significantly used as energy substrates, especially in starvation, **hypoglycemia** occurs due to impaired gluconeogenesis or excessive glucose consumption.
- Ketoacidosis is typical for *ketolysis* disorders.



Blood glucose regulation

Metabolism in mitochondria mainly concerns long-chain fatty acids, which enter the mitochondria via the *carnitine cycle*, and medium-chain fatty acids, which into the mitochondria they diffuse across the membrane.

Fatty acid metabolism disorders may include:

- carnitine cycle,
- β-oxidation of fatty acids,
- electron transfer to complex II (oxidation $FADH_2$ on FAD),
- synthesis of ketone bodies and ketolysis.

Deficiencies of enzymes involved in β-oxidation are typical symptoms after starvation - usually longer than 12 hours, which may be critical for patients - or even after increased exercise. The main symptom is **hypoglycemia**, **low concentrations of ketone bodies in the blood and urine** on an empty stomach, or **muscle weakness** and **rhabdomyolysis**.

Carnitine cycle disorders

Physiologically, long-chain fatty acids are transported to the mitochondria from the cytosol via the carnitine cycle: carnitine palmitoyl transferase 1 (CPT1) catalyzes the condensation of fatty acids with carnitine, acylcarnitine crosses the outer mitochondrial membrane, acylcarnitine translocase transfers acylcarnitine through the inner mitochondrial membrane free carnitine back. In the matrix, acylcarnitine is hydrolyzed by carnitine by palmitoyl transferase 2 (CPT2).

These enzymopathies can occur:

- **Carnitine palmitoyl transferase 1** - typical hypoglycemia on an empty stomach, heart and skeletal muscle are, unlike CPT2 deficiency, without a defect; **total carnitine 150-200 %**.
- **Carnitine palmitoyl transferase 2** - carnitine approx. 25–50 %, has two forms:
  1. **mild (adult) form** - rhabdomyolysis after exercise, starvation or cold exposure, myoglobinopathy;
  2. **severe (neonatal) form** - cardiomyopathy, muscle weakness, congenital malformations.
- **Carnitine acylcarnitine translocase** - fasting hypoketotic hypoglycemia, passing into coma, arrhythmias, apnea; frequent death in infancy.
- OCTN 2 - hypertrophic cardiomyopathy leading to heart failure; **plasma carnitine <2-5 %**, urinary carnitine loss; **dietary carnitine treatment**.

Disorders of β-oxidation

Deficits are possible:

- MCAD – **very common disease**, incidence in the UK and US 1: 10,000, starvation **life-threatening hypoglycemia**, frequent infections, manifestations in infancy, positive prognosis for survival, treatment: **starvation prevention**, corn starch nutrition; parenteral nutrition should be instituted for lethargy and vomiting leading to coma; (df. dgn. watch out for Reye's syndrome).
- VLCAD - hypoketonic hypoglycemia, cardiomyopathy, muscle weakness, decompensation of metabolism leads to coma.
- SCAD - Probably not a disease.
- Long chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD) - retinal degeneration, heterozygous mothers is affected by the so-called AFLP syndrome.

Disorders of ketone body synthesis and ketolysis

- Heredity AR.
- Ketone metabolism takes place in the mitochondria of the liver.
- **HMG-CoA synthase** catalyzes the condensation of acetoacetyl-CoA and acetyl-CoA to HMG-CoA,

which is cleaved in the presence of **HMG-CoA lyase** to acetyl-CoA and acetoacetate.

- Ketolysis is initiated by the transfer of CoA from succinyl-CoA to acetoacetate, which catalyzes **SCOT**. Acetoacetyl-CoA is formed, which is converted to acetyl-CoA with the participation of "acetoacetyl-CoA thiolase.

KETOGENESIS:

- Deficiency of **3-hydroxy-3-methylglutaryl-CoA synthase (HMG-CoA synthase)** - manifestations up to six years of age, coma, hepatomegaly, gastroenteritis, dicarboxylic aciduria. Immediate improvement after intravenous glucose administration, no long-term complications.
- Deficiency of **3-hydroxy-3-methylglutaryl-CoA lyase (HMG-CoA lyase)** manifestations up to the fifth day of birth, possibility of starvation or infection. Vomiting, hypotension, disorders consciousness, hyperammonemia, hepatomegaly. Possible complications pancreatitis, epilepsy, loss of central vision. In the blood hypoglycemia and hypoketonemia, 3-hydroxy-3-methylglutaric acid in the urine.

KETOLYSIS:

- Deficiency of **succinyl-CoA acetoacetyl-CoA transferase** - SCOT - first manifestations a few days after birth, recurrent attacks of severe acidosis, tachypnoea, hypotension, lethargy.
- **Acetoacetyl-CoA thiolase** deficiency - the first attacks of ketoacidosis in the first two years of life, associated with tachypnoea and vomiting, followed by dehydration and impaired consciousness, sometimes lead to mental retardation. Several patients had convulsions. Metabolic acidosis with ketonuria has been demonstrated in patients.
- *Treatment:* A high intake of carbohydrates in food and drink is necessary, as well as in the event of stress. Protein restriction is recommended because ketolysis enzymes are also involved in their metabolism (ketogenic AMK, eg leucine) and fat reduction. In acidosis, infusion bicarbonate is required.

- *Prognosis:* It's significantly better with diagnosis and increasing age. Attacks can be lethal.

Links

related articles

- Citric acid cycle
- Hereditary metabolic disorders

External links

- Mitochondrial disease (english wikipedia)

Reference

References

- {{#switch: book

|book =

```
  Incomplete publication citation. FERNANDES, John. Diagnosis and treatment of hereditary metabolic disorders. Prague : Triton, 2008. pp. 576-580. 978-80-7262-438-6.
```

|collection =

```
  Incomplete citation of contribution in proceedings. FERNANDES, John. Diagnosis and treatment of hereditary metabolic disorders. Prague : Triton, 2008. pp. 576-580. {{
  #if: 978-80-7387-096-6 |978-80-7262-438-6} }
  |article =
  Incomplete article citation.  FERNANDES, John. 2008, year 2008, pp. 576-580,
```

|web =

```
  Incomplete site citation. FERNANDES, John. Triton, ©2008.
```

|cd =

```
  Incomplete carrier citation. FERNANDES, John. Triton, ©2008.
```

|db =

Incomplete database citation. Triton, ©2008.

|corporate_literature =

FERNANDES, John. *Diagnosis and treatment of hereditary metabolic disorders.* Prague : Triton, 2008. 978-80-7262-438-6} }, s. 576-580.

- {{#switch: book

|book =

Incomplete publication citation. MURRAY, Robert K., Daryl K. GRANNER and Peter A. MAYES, et al. *Harper biochemistry.* Jinočany : H & H, 2002. 872 s. 4; 978-80-7262-438-6.

|collection =

Incomplete citation of contribution in proceedings. MURRAY, Robert K., Daryl K. GRANNER and Peter A. MAYES, et al. *Harper biochemistry.* Jinočany : H & H, 2002. 872 s. 4; {{
#if: 80-7319-013-3 |978-80-7262-438-6} }
|article =
Incomplete article citation. MURRAY, Robert K., Daryl K. GRANNER and Peter A. MAYES, et al. 2002, year 2002,

|web =

Incomplete site citation. MURRAY, Robert K., Daryl K. GRANNER and Peter A. MAYES, et al. H & H, ©2002.

|cd =

Incomplete carrier citation. MURRAY, Robert K., Daryl K. GRANNER and Peter A. MAYES, et al. H & H, ©2002.

|db =

Incomplete database citation. H & H, ©2002.

|corporate_literature =

MURRAY, Robert K., Daryl K. GRANNER and Peter A. MAYES, et al. *Harper biochemistry.* Jinočany : H & H, 2002. 872 s. 4; 978-80-7262-438-6} }

}}